CARCINOGENICITY OF ORTHOAMINOAZOTOLUENE FOR THE MOUSE INTESTINES

V. I. Kaledin, G. V. Alekseeva,
and A. I. Volkova

UDC 615.277.4:547.556.33

The carcinogenic activity of orthoaminoazotoluene against intestinal tissues of A/He mice was discovered. Intestinal tumors developed in 19 of 60 mice receiving the carcinogen subcutaneously. All tumors were located in the cecum and consisted of adenomas and mucus-secreting adenocarcinomas.

KEY WORDS: mice; orthoaminoazotoluene; carcinogenesis; intestinal tumors.

Orthoaminoazotoluene (OAT), usually used in experimental oncology as a hepatotropic carcinogen, also induces vascular and lung tumors in mice [1, 2]. There are no data in the literature on the carcinogenicity of this compound for tissues of the gastrointestinal tract. The writers observed the development of tumors of the cecum in A/He mice receiving OAT for long periods.

EXPERIMENTAL METHOD

Male A/He mice reared at the Institute of Cytology and Genetics, Siberian Division, Academy of Sciences of the USSR, were used. The animals were kept in metal cages in groups of 8 to 10 animals per cage on an ordinary laboratory diet. At the age of two months a capsule containing 10 mg crystalline OAT, from the Khar'kov Chemical Reagent Factory, was implanted subcutaneously into the mice in the dorsal region. A further seven implantations of the carcinogen were given at monthly intervals. Altogether each animal thus received 80 mg OAT. The mice remained under observation until death. Mice which died were autopsied, the presence of macroscopically visible tumors was noted, and organs affected with tumors were fixed in 10% formalin. Paraffin sections were cut from the fixed material, stained with hematoxylin-eosin, and examined under the microscope.

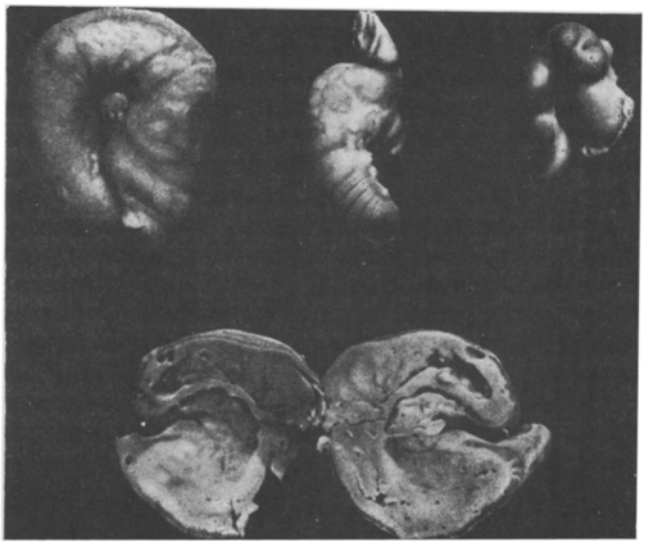

Fig. 1. Tumors of the cecum induced by OAT in mice of line A/He.

Laboratory of Genetics of Cancer, Institute of Cytology and Genetics, Siberian Division, Academy of Sciences of the USSR, Novosibirsk. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 10, pp. 476-477, October, 1978. Original article submitted June 20, 1977.

 0007-4888/78/8610-1374$07.50

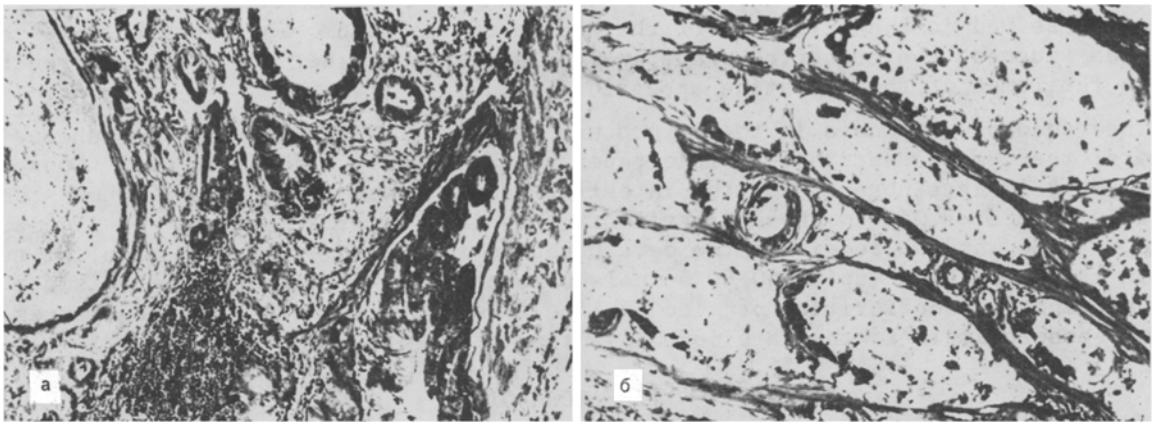

Fig. 2. Adenocarcinoma of cecum in A/He mouse receiving OAT: a) atypical proliferation of epithelium of gland and formation of cystic cavity; b) multiple cysts filled with mucus and cell debris. Hematoxylin-eosin, 70×.

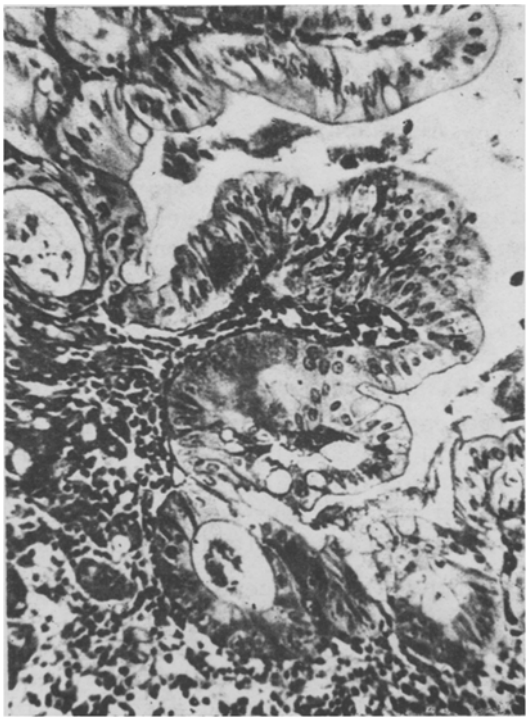

Fig. 3. Proliferative-destructive changes in mucosa of cecum in mouse receiving OAT. Hematoxylin-eosin, 140×.

EXPERIMENTAL RESULTS

All 60 mice receiving the carcinogen died on average 435 ± 13 days after the first adminstration of OAT. The chief cause of death of the animals was tumors of the liver. However, besides tumors of the liver, 19 animals (31.7%) also had intestinal tumors. These tumors were located exclusively in the cecum and consisted of globular or diffuse whitish growths, often involving the whole intestine and obstructing its lumen (Fig. 1). In some cases the weight of the tumors exceeded 1.5 g.

Microscopically, the tumors consisted of adenomas and mucus-secreting adenocarcinomas. They were multiple growths of glandular epithelium, forming atypical intestinal glands. The glands were extremely abnormal in shape and they varied in size within very wide limits. The epithelium in the large glands easily desquamated and they were converted into cysts filled with mucus and desquamated living and degenerating cells (Fig. 2a). Frequently the process of mucus formation occurred almost throughout the tumor (Fig. 2b). Substantial disturbances

also were observed in the structure of the mucosa of the cecum. The proliferative zone in the crypts was widened, the number of wandering cells was increased, and atypical growths projecting into the lumen of the intestine appeared (Fig. 3).

Since according to data in the literature A/He mice do not develop spontaneous intestinal tumors, the tumors described in this paper were evidently induced by OAT. Consequently, this compound is carcinogenic for the intestine also. However, intestinal tumors develop under the influence of OAT in these experiments only in A/He mice. In mice of lines CC57BR, C57BL/6, C3H/He, and DD receiving the carcinogen in the same way as A/He mice, no tumors were found in this situation (up to 40-60 animals of each line were studied). It is not clear with what genetic peculiarities of mice of line A/He the sensitivity of the tissues of the cecum of these animals to the carcinogenic action of OAT is linked.

LITERATURE CITED

1. H. B. Andervont, H. G. Grady, and J. E. Edwards, J. Nat. Cancer Inst., 3, 13 (1942).
2. Y. Nishizuka, K. Ito, and K. Nakakuki, Gan (Tokyo), 56, 135 (1965).

PATTERN OF TRANSPLACENTAL PENETRATION OF 7,12-DIMETHYLBENZ(a)ANTHRACENE AND ITS DISTRIBUTION IN THE FETAL ORGANS IN MAN

L. N. Baranova and V. A. Aleksandrov

UDC 612.649:612.388-064:615.277.4

On the 21st day of pregnancy 7,12-dimethylbenz(a)anthracene (DMBA) was injected into female rats in a dose of 15 mg/kg and its concentration in the liver of the pregnant rats, the placenta, and the fetus was determined by a fluorescence-spectral method. The maximal concentration was rapidly reached (after 10-15 min) in the liver of the pregnant rats (45 mg/kg) and placenta (6.3 mg/kg), but more slowly (after 1 h) in the tissues of the fetus (2.4 μg/kg). Clearance of the carcinogen from all the tissues took place relatively slowly (in about 5 h). DMBA was shown to be irregularly distributed in the different organs of the fetus 1 h after its injection into the pregnant rats: maximally in the fetal liver, minimally in the carcass, compared with its concentration in other organs (kidneys, lungs, brain, intestine). The results do not correlate with data showing the development of tumors predominantly in the kidneys and nervous system of rats following transplacental exposure to DMBA.

KEY WORDS: 7,12-dimethylbenz(a)anthracene; placental barrier.

The study of the placental barrier in rats and mice has demonstrated its high permeability to carcinogenic polycyclic hydrocarbons and also certain general principles regarding their accumulation in the fetal tissues and their subsequent elimination. It is interesting to study the pattern of accumulation of carcinogens in the various organs of the fetus. This problem has a direct bearing on the mechanisms of transplacental carcinogenesis, i.e., the phenomenon of development of tumors in the progeny as a result of administration of chemical carcinogens to the mother during pregnancy. It was shown previously that following transplacental exposure (on the 21st day of pregnancy) to 7,12-dimethylbenz(a)anthracene (DMBA), injected intravenously in a dose of 15 mg/kg, tumors mainly of the nervous system and kidneys developed in the progeny of the rats [1]. After administration of the compound at the same period of pregnancy but in a larger dose (25 mg/kg) the penetration of DMBA through the placenta and the dynamics of its entry into the fetus were studied in detail in rats [2]. Under these circumstances, a fluorescence-spectral method was used to determine the concentration in the tissues.

Laboratory of Biophysics and Laboratory of Experimental Tumors, Professor N. N. Petrov Research Institute of Oncology, Ministry of Health of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 10, pp. 477-479, October, 1978. Original article submitted December 22, 1977.

 0007-4888/78/8610-1376$07.50